CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 074792

Trade Name Glyburide

Generic Name Glyburide

Sponsor Mylan

Approval Date: December 19, 1996

ANDA 74-792

DEC 16 1996

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated November 21, 1995 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets (Micronized), 1.5 mg and 3 mg.

Reference is also made to your amendments dated May 8, September 27, and October 17, 1996.

Your application contains patent certifications to patent #4735805 and patent #4916163 under Section 505(j)(2)(A)(vii)(IV) of the act. Section 505(j)(4)(B)(iii) of the act provides that "approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received." You have notified FDA that Mylan Pharmaceuticals has complied with the requirements of Section 505(j)(2)(B) of the act. No action for patent infringement was brought against Mylan Pharmaceuticals within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Glyburide Tablets (Micronized), 1.5 mg and 3 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Glynase Tablets 1.5 mg and 3 mg, respectively, of Pharmacia and Upjohn Company. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

cc: ANDA #74-792
ANDA #74-792/Division file
Field Copy
HFD-600/Reading file
HFD-82
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:

HFD-625/SBrown/10-18-96
HFD-613/CHolquist/10-29-96
HFD-613/A.Vezza for JGrace/10-29-96
HFD-625/MSmela/10-22-96
HFD-617/SO'Keefe, PM/11-15-96
X:\new\firmsam\mylan\ltrs&rev\74792.r#3
FT by MM December 17, 1996
Approval Letter

MYLAN PHARMACEUTICALS INC.

GLYBURIDE TABLETS, 3MG
ANDA 74-792

N 3 0378-1125-10 9

3 mg

Each tablet contains:
Glyburide ...... 3 mg

NDC 0378-1125-10

MYLAN®

TABLETS
(micronized)

1000 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See package insert for complete product information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1125C

N 3 0378-1125-10 9

3 mg

Each tablet contains:
Glyburide ...... 3 mg

NDC 0378-1125-10

MYLAN®

TABLETS
(micronized)

1000 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1125C

MYLAN PHARMACEUTICALS INC.

GLYBURIDE TABLETS, 3MG
ANDA 74-792

N 3 0378-1125-01 7

3 mg

Each tablet contains:
Glyburide ...... 3 mg

NDC 0378-1125-01

MYLAN®

TABLETS
(micronized)

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

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Usual Dosage: See package insert for complete product information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1125A

N 3 0378-1125-01 7

3 mg

Each tablet contains:
Glyburide ...... 3 mg

NDC 0378-1125-01

MYLAN®

TABLETS
(micronized)

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1125A

N 3 0378-1125-01 7

3 mg

Each tablet contains:
Glyburide ...... 3 mg

NDC 0378-1125-01

MYLAN®

TABLETS
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Usual Dosage: See package insert for complete product information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1125A

MYLAN PHARMACEUTICALS INC.

GLYBURIDE TABLETS, 1.5MG
ANDA 74-792

N 3 0378-1113-01 4

1.5 mg

Each tablet contains:
Glyburide .... 1.5 mg

NDC 0378-1113-01

MYLAN®

GLYBURIDE TABLETS
(micronized)
1.5 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See package insert for complete product information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1113A

N 3 0378-1113-01 4

1.5 mg

Each tablet contains:
Glyburide .... 1.5 mg

NDC 0378-1113-01

MYLAN®

GLYBURIDE TABLETS
(micronized)
1.5 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See package insert for complete product information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1113A

N 3 0378-1113-01 4

1.5 mg

Each tablet contains:
Glyburide .... 1.5 mg

NDC 0378-1113-01

MYLAN®

GLYBURIDE TABLETS
(micronized)
1.5 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

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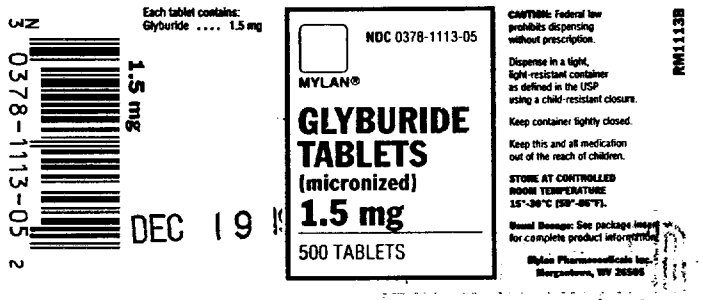
Usual Dosage: See package insert for complete product information.

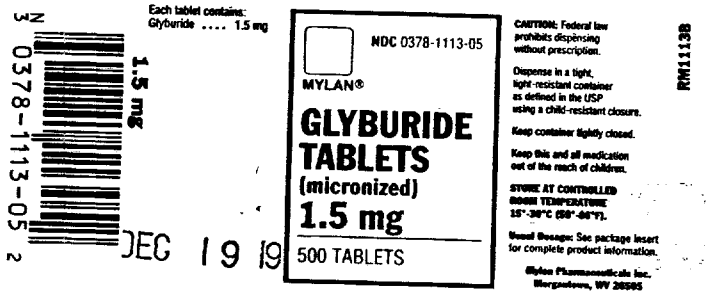
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

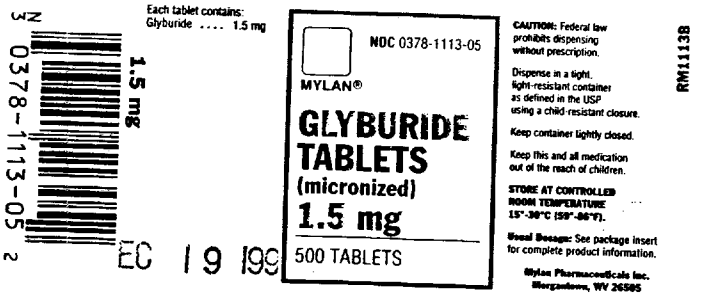
RM1113A

MYLAN PHARMACEUTICALS INC.

GLYBURIDE TABLETS, 1.5MG
ANDA 74-792







GLY:R1

GLYBURIDE TABLETS (micronized) 1.5 mg and 3 mg

DESCRIPTION: Glyburide tablets (micronized) contain smaller particle size. Glyburide is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound.

Each tablet, for oral administration, contains 1.5 mg or 3 mg of micronized glyburide. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, pregelatinized starch, and sodium lauryl sulfate. In addition, the 3 mg tablets contain the following ingredient: D&C Yellow #10 Aluminum Lake.

The chemical name for glyburide is 1-[[p-[2-(5-Chloro-*o*-anisamido) ethyl] phenyl]-sulfonyl]-3-cyclohexylurea and the molecular weight is 494.01. It has the following structural and molecular formula:

Glyburide

$C_{23}H_{28}ClN_3O_5S$

CLINICAL PHARMACOLOGY: Actions: Glyburide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Some patients who are initially responsive to oral hypoglycemic drugs, including glyburide, may become unresponsive or poorly responsive over time. Alternatively, glyburide may be effective in some patients who have become unresponsive to one or more other sulfonylurea drugs.

In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance. Disulfiram-like reactions have very rarely been reported in patients treated with glyburide.

Pharmacokinetics: Single dose studies with glyburide tablets (micronized) in normal subjects demon-

may be effective in some patients who have become unresponsive to one or more other sulfonylurea drugs.

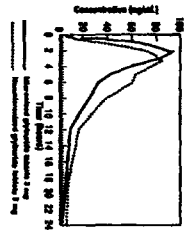
In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance. Disulfiram-like reactions have very rarely been reported in patients treated with glyburide.

Pharmacokinetics: Single dose studies with glyburide tablets (micronized) in normal subjects demonstrate significant absorption of glyburide within one hour, peak drug levels at about two to three hours, and low but detectable levels at twenty-four hours.

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from nonmicronized glyburide tablets 5 mg. Therefore, the patient should be retitrated.

It has been reported that in a single-dose bioavailability study (see Figure A) in which subjects received micronized glyburide tablets 3 mg and nonmicronized glyburide tablets 5 mg with breakfast, the peak of the mean serum glyburide concentration-time curve was 97.2 ng/mL for the micronized glyburide tablets 3 mg and 87.5 ng/mL for nonmicronized glyburide tablets 5 mg. The mean of the individual maximum serum concentration values of glyburide (C_{max}) from micronized glyburide tablets 3 mg was 106 ng/mL and that from nonmicronized glyburide tablets was 104 ng/mL. The mean glyburide area under the serum concentration-time curve (AUC) for this study was 568 ng x hr/mL for micronized glyburide tablets 3 mg and 746 ng x hr/mL for nonmicronized glyburide tablets 5 mg.

Figure A



Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no buildup of drug in tissue depots.

The serum concentration of glyburide in normal subjects decreased with a half-life of about four hours.

In single dose studies in fasting normal subjects who were administered glyburide tablets (micronized) in doses ranging from 1.25 mg to 5 mg, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning doses in nonfasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A one year study of diabetic patients treated with glyburide showed no reliable correlation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic,

(1.4000th and 1.400th as active, respectively, as glyburide) in rabbits.

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Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide in clinical use.

INDICATIONS AND USAGE: Glyburide tablets (micronized) are indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of glyburide must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitution or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of glyburide.

During maintenance programs, glyburide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgment should be based on regular clinical and laboratory evaluations.

In considering the use of glyburide in asymptomatic patients, it should be recognized that controlling blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS: Glyburide is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. Type I diabetes mellitus, as sole therapy.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19 (Suppl. 2):747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite

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Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from nonmicronized glyburide tablets 5 mg. Therefore, patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents.

General: ***Hypoglycemia:*** All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated drug levels of glyburide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose lowering drug is used.

Loss Of Control Of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. At such times it may be necessary to discontinue glyburide and administer insulin.

The effectiveness of any hypoglycemic drug, including glyburide, in lowering blood glucose to a desired level decreases in many patients over a period of time which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when glyburide is first given. Adequate adjustment of

sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

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Information For Patients: Patients should be informed of the potential risks and advantages of glyburide and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

Laboratory Tests: Therapeutic response to glyburide tablets (micronized) should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving glyburide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for loss of control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glyburide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for hypoglycemia.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism of action for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay.

No drug-related effects were noted in any of the criteria evaluated in the two-year oncogenicity study of glyburide in mice.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 500 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glyburide is used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers: Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Hypoglycemia: See PRECAUTIONS and OVERDOSAGE Sections.

Gastrointestinal Reactions: Cholestatic jaundice and hepatitis may

discontinued at least two weeks before the expected delivery date.

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Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Hypoglycemia: See PRECAUTIONS and OVERDOSAGE Sections.

Gastrointestinal Reactions: Cholestatic jaundice and hepatitis may occur rarely; glyburide should be discontinued if this occurs.

Liver function abnormalities, including isolated transaminase elevations, have been reported.

Gastrointestinal disturbances, e.g., nausea, epigastric fullness, and heartburn are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.5% of treated patients during clinical trials. These may be transient and may disappear despite continued use of glyburide. If skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with glyburide and disulfiram-like reactions have been reported very rarely.

Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions: Changes in accommodation and/or blurred vision have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia and vasculitis have been reported.

OVERDOSAGE: Overdosage of sulfonylureas, including glyburide, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION: Patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents.

tablets (micronized) should be observed. A maintenance dose of 3 mg of glyburide tablets (micronized) provide approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 5 mg of non-micronized glyburide, 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of glyburide tablets (micronized) 3 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of glyburide tablets (micronized) in increments of 0.75 to 1.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and glyburide are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

Maximum Dose: Daily doses of more than 12 mg are not recommended.

Dosage Interval: Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 6 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations: Glyburide is not recommended for use in pregnancy or for use in children.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See PRECAUTIONS Section).

HOW SUPPLIED: Glyburide tablets (micronized) are available containing 1.5 mg and 3 mg of glyburide as follows:

The 1.5 mg tablets are white, scored, oval tablets marked with M 113 on one side and blank on the other side. They are available as follows:

NDC 0378-1113-01
bottles of 100 tablets
NDC 0378-1113-05
bottles of 500 tablets

The 3 mg tablets are light yellow, scored, oval tablets marked with M 125 on one side and blank on the other side. They are available as follows:

NDC 0378-1125-01
bottles of 100 tablets
NDC 0378-1125-10
bottles of 1000 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30° C (59°-86° F).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED MAY 1996
GLY:R1

D IV

1. CHEMISTRY REVIEW NO.3

2. ANDA # 74-792

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Glyburide

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

November 21, 1995:	Original submission
December 8, 1995:	ONC
May 8, 1996:	Bio Info.
June 6, 1996:	amendment responding to NAL dated 5/13/96
July 2, 1996:	NC (response to bioequivalence's letter dated June 26, 1996)
*August 30, 1996:	ONC (patents are invalid)
*September 6, 1996:	ONC (notice of certification to patent holders that patents are invalid)
*September 27, 1996:	amendment responding to NAL dated 8/30/96
*October 17, 1996:	amendment responding to laboratory comments

10. PHARMACOLOGICAL CATEGORY

Hypoglycemic

11. Rx or OTC

Rx

12. RELATED NDA/DMFs

See review #1.

13. DOSAGE FORM

Tablet (micronized)

14. POTENCY

1.5 mg and 3 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

As requested in our NAL dated August 30, 1996 applicant has noted and acknowledged the following:

> A satisfactory methods validation for the finished dosage form to support the ANDA is required prior to approval.

18. CONCLUSIONS AND RECOMMENDATIONS

All deficiencies are satisfied. The ANDA is approvable.

19. REVIEWER: DATE COMPLETED:

Shirley S. Brown October 18, 1996

cc: ANDA #74-792
ANDA #74-792/Division File
Field Copy

Endorsements:

HFD-625/SBrown/10-18-96

HFD-625/MSmela/10-22-96

X:\new\firmsam\mylan\ltrs&rev\74792.r#3
F/T by MM November 18, 1996
APPROVABLE

ANDA 74-792

Mylan Pharmaceuticals Inc.
Attention: W. Bradley McMillen
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

JUN 25 1996

Dear Sir:

This is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets, 1.5 mg and 3 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of borate buffer, pH 9.5 at 37° using USP 23 apparatus 2 (paddle) at 75 rpm. The test products should meet the following specifications:

   Not less than of the labeled amount of glyburide in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 20 1996

Glyburide
Tablets, 1.5 mg & 3 mg
ANDA # 74-792
Reviewer: L. Chuang

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
November 21, 1995
May 8, 1996

Review of Two Bioequivalence Studies, Waiver Request and Dissolution Data

Introduction:

Glyburide is an oral hypoglycemic agent effective in diabetic patients who have retained some degree of pancreatic insulin-releasing function.

The bioavailability of glyburide is 40-45% with the early formulation and 100% with the improved formulations. It is 98--99% bound to albumin. After an oral dose of 3 mg, the C_{max} was 106 ng/mL, T_{max} was 2-3 hours and $T_{1/2}$ was 4 hours. It is extensively metabolized in the liver mainly by the hydroxylation of the cyclohexyl ring. The hydroxylated metabolites have no significant hypoglycemic activity and they are excreted equally in the urine and the bile.

Glyburide is usually administered as a single daily dose each morning with breakfast or with the first main meal. The recommended initial adult dose of glyburide is 2.5-5 mg daily. The maximum recommended single daily dose is 10 mg and the maximum recommended total daily dose is 20 mg.

The listed reference product of glyburide is Glynase^R 6 mg tablet manufactured by The Upjohn Company. Glynase^R tablet is also marketed as 3 mg tablet by the same company.

Bioequivalence Study - Fasting:

The objective of this study is to assess the bioequivalence of the firm's glyburide 3 mg tablet and Glynase^R 3 mg tablet manufactured by Upjohn Co. in fasting volunteers.

The clinical portion of the study was conducted at the

during 06/03-07/03/95. The analytical portion of the study was conducted at the

The study was conducted in a randomized, 2-treatment, 2-period, single dose crossover design. The approved the protocol and the informed consent form on 02/16/95.

It was designed in the protocol to have at least 30 volunteers completed the study. Forty-five (45) subjects were recruited. The inclusion and exclusion criteria are listed below:

Inclusion Criteria:

1. Males between 19-55 years old and within ±10% of ideal body weight.
2. Normal physical examination results and medical history.
3. Laboratory evaluation within normal limits. The tests included blood count, electrolytes, liver function, kidney function, measurements of uric acid, cholesterol (allowed to be outside limits) and iron, urinalysis, and urine drug screen; all conducted within 2 weeks of the study.

Exclusion Criteria:

1. Receipt of investigational drug within 4 weeks of the study.
2. Using tobacco.
3. Acute illness or surgery within 4 weeks of the study.
4. History of allergy to sulfonylurea-related drugs.
5. Presence of any pathological conditions of any part of the body.
6. Any medication within 2 weeks of the study.
7. Ingestion of alcohol beverages of caffeine- or xanthine-containing food or beverages within 48 hours of the study.
8. History of alcohol or drug abuse, cardiac arrhythmias, psychotropic agents usage, or hepatitis.
9. Donation of blood within 3 months or blood products within 14 days.

During the study period (including the washout period), no concurrent diseases or medications were allowed.

Of the 45 subjects recruited , 6 did not report for phase 1 dosing. The remaining 39 subjects (33 white, 4 Asian-Pacific and 2 Hispanic males) were dosed in 2 groups due to the number of volunteers that did not report for phase 1. For group A (subjects 1-29), phase 1 was conducted on 06/03/95 and phase 2 on 06/17/95. For group B (subjects 30-39), phase 1 was conducted on 06/17/95 and phase 2 on 7/1/95.

Subjects were fasted from 10 pm on the day prior to dosing until lunch the next day. At 8 am on the day of dosing, each subject was assigned randomly to one of the following treatments:

Treatment A - Reference Drug: Glynase^{R} tablets, 2 x 3 mg, Upjohn Co. lot #103JC, potency 101.7%, expires 4/97.

Treatment B - Test Drug: Glyburide tablets, 2 x 3 mg, Mylan lot #2B002D, potency 100.5%, batch size of

Each treatment was taken with 240 mL of apple juice to minimize hypoglycemic effects of glyburide.

Each subject was given 2 ounces of apple juice every 15 minutes during the first 4 hours after dosing. Blood samples (10 ml each) were collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing. Plasma samples were prepared and immediately frozen.

All subjects remained ambulatory during the study but were not permitted to engage in strenuous exercise. Vital signs were measured hourly for the first 8 hours and at 12, 24, 36 and 48 hours after dosing. Lunch was served at 4 hours after dosing. All participants remained at a monitored center for at least 24 hours after dosing and returned to the testing center for period 2 after a 14-day washout period. At the conclusion of the study, all subjects underwent the same physical and laboratory evaluation made at the start of the study.

Analytical Method:

Results:

Out of the 39 subjects entered phase 1, 37 completed the study. Subject #9 failed to report for phase 2 (treatment A) dosing due to personal reason (not study related). Subject #30 was discontinued during period 1 (treatment B) after 48 hour blood collection due to adverse experiences which were not study related, he reported that he had blood in his urine. This problem was resolved in 4 days. Another volunteer, subject #14, did not report to have his 36 hour blood draw during period 2 (treatment B).

No clinically significant abnormalities were detected during the post-study physical and laboratory evaluation. Forty-four (44) adverse events were reported, 21 occurred during treatment A and 23 during treatment B. The symptoms were headache, perspiring, clammy skin, lightheadedness, shakiness, diaphoretic, nausea, pale, confusion, leg weakness, vomiting and blood in urine. Except headache and blood in urine, these symptoms were probably related to the study drug administered.

Of the 37 subjects completed the study, 20 were in the sequence of AB and 17 were BA. Only the analytical results from 36 subjects were reported, the result of subject #29, who was in sequence AB, was not reported.

Of the 1367 plasma samples received for the assay of glyburide, 19 were reassayed, all had no initial assay values because of sample loss during extraction, power failure, abnormal internal standard response, instrument malfunction or process deviation. The repeat assay value was reported for each repeated sample.

Five (5) plasma samples were reported as "missing" due to insufficient plasma quantity, i.e. subject # 26, hour 1, 3.5, and 10 during treatment A (T_{max} was 4.5 hours), and hour 48 during treatment B; and subject #27, hour 6 during treatment B (T_{max} was 1.5 hours).

The mean plasma concentrations of glyburide at each sampling point after both treatments in 36 subjects and the mean pharmacokinetic parameters are presented below in Table 1.

Table 1: Mean (C.V.%) Plasma Glyburide Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 36[a] -- Fasting Study)

Time (hour)	Upjohn (Treatment A)	Mylan (Treatment B)
0	0	0
0.5	12.33 (11.9)	17.98 (14.4)
1.0	25.70[b] (12.1)	51.96 (9.9)
1.5	34.62 (13.2)	75.85 (8.9)
2.0	43.87 (15.4)	89.36 (8.3)
2.5	70.57 (15.4)	101.95 (8.5)
3.0	87.59 (13.5)	111.95 (6.8)
3.5	91.96[b] (12.2)	118.91 (7.2)
4.0	91.73 (10.6)	117.60 (7.9)
4.5	100.47 (7.0)	112.21 (7.4)
5.0	90.91 (7.2)	86.59 (7.5)
6.0	74.76 (12.7)	58.16[b] (6.7)
8.0	51.51 (12.3)	38.79 (8.4)
10.0	35.85[b] (8.8)	31.49 (10.2)
12.0	29.03 (7.4)	32.18 (12.7)
16.0	23.50 (11.3)	18.83 (9.2)
24.0	13.16 (8.0)	9.85 (9.3)
36.0	3.27 (20.5)	1.88[b] (36.2)
48.0	0.83 (44.6)	0.41[b] (60.1)

AUC_{0-t} (ng*hr/mL)	992.91 (30.2)	975.45 (25.8)
$LNAUC_{0-t}$	6.86 (953.38[c])	6.85 (943.88[c])
AUC_{0-inf} (ng*hr/mL)	1135.07 (28.0)	1084.89 (24.4)
$LNAUC_{0-inf}$	7.00 (1096.63[c])	6.96 (1053.63[c])
C_{max} (ng/mL)	161.67 (33.3)	158.53 (34.7)
LNC_{max}	5.04 (154.47[c])	5.02 (151.41[c])
T_{max} (hour)	4.01 (31.2)	3.74 (48.9)
$T_{1/2}$ (hour)	10.84 (39.7)	8.83 (52.7)

a : unless otherwise indicated
b : n = 35
c : Geometric Mean

Analysis of Variance was first performed on each pharmacokinetic parameter with a group effect model including effects for **group**, sequence, **sequence*group**, **sub(seq*group)**, treatment and period. Test hypothesis using **sub(seq*group)** as an error term was also conducted. No significant group effect was detected for any of the parameters. The ANOVA was conducted again without the group effect, the results showed no significant effect for any of the parameters.

However, the firm's's ANOVA model had only 2 levels of period, yet there were 3 periods in the study: 06/03/95, 06/17/95 and 07/01/95.

The LS means of all 3 untransformed and log transformed pharmacokinetic parameters, ratio of these means and the 90% confidence interval of test product versus reference product, using the firm's ANOVA model of 2 periods, are presented in Table 2.

Table 2: Statistical Analysis -- Fasting Study

Parameter	LS Means (Mylan)	LS Means (Upjohn)	T/R	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	973.90	992.89	0.98	(0.904; 1.058)
AUC_{0-inf} (ng*hr/mL)	1083.19	1132.36	0.96	(0.874; 1.039)
C_{max} (ng/mL)	159.21	162.46	0.98	(0.888; 1.072)
$LNAUC_{0-t}$	6.8493 (943.22[a])	6.8575 (950.99[a])	0.99[b]	(0.920; 1.067)

$LNAUC_{0-inf}$	6.9577 (1051.21[a])	6.9934 (1089.42[a])	0.96[b]	(0.884; 1.053)
LNC_{max}	5.0263 (152.37[a])	5.0418 (154.75[a])	0.98[b]	(0.890; 1.089)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The calculations for all the pharmacokinetic parameters and 90% confidence intervals were confirmed by the reviewer.

2. The ANOVA model used by the firm to obtain statistical results is not appropriate. On 04/22/96, it was recommended to the firm through telephone conference that the period should be coded as 1, 2, or 3 since there were 3 periods in the study, i.e., 06/03/95, 06/17/95 and 07/01/95, or to include period in the model as PER(GROUP).

   The sponsor's response was received on 05/08/96. ANOVA was conducted using 3 periods and including group effect.

   Since no significant group effect was detected previously, the reviewer conducted ANOVA with 3 periods and including effects for sequence, sub(seq), period, and treatment. Test hypothesis using sub(seq) as an error term was also conducted. The results showed no significant effect for any of the parameters. The LS means and 90% confidence intervals calculated with this new ANOVA method are presented below in Table 3:

Table 3: Statistical Analysis -- Fasting Study -- 3-period model

Parameter	LS Means (Mylan-Test)	LS Means (Upjohn-Reference)	T/R	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	974.01	992.32	0.98	(0.904; 1.058)
AUC_{0-inf} (ng*hr/mL)	1047.58	1093.65	0.96	(0.874; 1.039)
C_{max} (ng/mL)	158.61	161.75	0.98	(0.888; 1.072)
$LNAUC_{0-t}$	6.8514 (945.20[a])	6.8590 (952.41[a])	0.99[b]	(0.920; 1.067)
$LNAUC_{0-inf}$	6.9294 (1021.88[a])	6.9624 (1056.16[a])	0.97[b]	(0.884; 1.053)
LNC_{max}	5.0314 (153.15[a])	5.0469 (155.55[a])	0.98[b]	(0.890; 1.089)

a = Geometric Mean
b = Ratio of Geometric Means

3. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max}, obtained either with the 2-period ANOVA or the 3-period ANOVA, are all within the 80-125% limits.

4. The results of the fasting study are acceptable.

Bioequivalence Study - Non-Fasting:

The objective of this study is to assess the bioequivalence of the firm's glyburide 3 mg tablet and Glynase® 3 mg tablet manufactured by Upjohn Co. in non-fasting volunteers.

The clinical portion of the study was conducted at the

during 07/20-08/19/95. The analytical portion of the study was conducted at the Pharmacokinetics Laboratory of Mylan Pharmaceuticals in Morgantown, WV during 08/24-09/14/95 by P. K. Noonan, Ph.D..

The study was conducted in a randomized, 3-treatment, 3-period, single dose crossover design. The approved the protocol and the informed consent form on 02/16/95.

It was designed in the protocol to have at least 18 volunteers completed the study. Twenty (20) subjects (15 white, 3 Asian-Pacific and 2 black males) were recruited. The inclusion and exclusion criteria were the same as those listed in the fasting study except the age range was 19-50 instead of 19-55 years.

During the study (including the washout period), no concurrent diseases or medications are allowed.

Subjects were fasted from 10 pm on the day prior to dosing. At 8 am on the day of dosing, each subject received one of the following treatments according to one of the 6 sequences (ABC, ACB, BAC, BCA, CAB and CBA) that subject had randomly been assigned to:

Treatment A - Reference Drug: Glynase® tablets, 2 x 3 mg, Upjohn Co. lot #103JC, potency 101.7%, expires 4/97, given 30 minutes after a standardized breakfast*.

Treatment B - Test Drug: Glyburide tablets, 2 x 3 mg, Mylan lot #2B002D, potency 100.5%, batch size of , given 30 minutes after

a standardized breakfast*.

Treatment C - Test Drug: Glyburide tablets, 2 x 3 mg, Mylan lot #2B002D, potency 100.5%, batch size of [redacted] tablets, given under fasting condition.

* = 1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 serving hash brown potatoes, 6 0z orange juice and 8 oz whole milk.

Each treatment was taken with 240 mL of apple juice to minimize hypoglycemic effects of glyburide. Each subject was given 2 ounces of apple juice every 15 minutes during the first 4 hours after dosing. Blood samples (10 ml each) were collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing. Plasma samples were prepared and immediately frozen.

All subjects remained ambulatory during the study but were not permitted to engage in strenuous exercise. Vital signs were measured hourly for the first 8 hours and at 12, 24, 36 and 48 hours after dosing. Lunch was served at 4 hours after dosing. All participants remained at a monitored center for at least 24 hours after dosing and returned to the testing center for period 2 after a 14-day washout period. At the conclusion of the study, all subjects underwent the same physical and laboratory evaluation made at the start of the study.

Analytical Method:

Results:

All 20 subjects recruited completed the study.

No clinically significant abnormalities were detected during the post-study physical and laboratory evaluation. Fifteen (15) adverse events were reported, 3 occurred during treatment A, 5 during treatment B and 7 during treatment C. The symptoms were headache, perspiration, dizziness, lightheadedness, heartburn, sweating, and feeling hot and tired or warm. Except 1 case of headache,

all the adverse reactions were probably related to the study drug administered.

Of the 760 plasma samples received for the assay of glyburide, 24 were reassayed, all had no initial assay values because of sample loss during extraction, abnormal internal standard response, bad sensitivity and poor chromatography. The repeat assay value was reported for each repeated sample.

Two (2) plasma samples were reported as "quantity not sufficient", i.e. subject #19, hour 36 and 48 during treatment A.

The mean plasma concentrations of glyburide at each sampling point after each treatment in 20 subjects and the mean pharmacokinetic parameters are presented below in Table 4.

Table 4: Mean (C.V.%) Plasma Glyburide Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 20* -- Non-Fasting Study)

Time (hour)	Upjohn - Non-Fasting (Treatment A)	Mylan - Non-Fasting (Treatment B)	Mylan - Fasting (Treatment C)
0	0	0	0
0.5	13.40 (34)	22.08 (22)	19.44 (15)
1.0	60.02 (26)	87.17 (16)	48.62 (13)
1.5	98.93 (16)	124.62 (12)	66.88 (12)
2.0	118.07 (11)	146.70 (6.8)	74.49 (13)
2.5	133.95 (8.8)	148.84 (5.6)	80.61 (12)
3.0	131.69 (7.4)	142.32 (5.4)	75.73 (13)
3.5	119.99 (7.8)	123.66 (4.8)	69.13 (12)
4.0	108.44 (7.3)	111.40 (5.3)	63.50 (14)
4.5	108.09 (7.2)	104.49 (5.2)	65.12 (16)
5.0	90.70 (9.5)	88.37 (8.2)	54.54 (14)
6.0	77.98 (11)	70.25 (9.7)	42.03 (14)
8.0	55.08 (11)	48.93 (13)	41.44 (18)
10.0	36.94 (11)	30.19 (10)	50.62 (16)
12.0	21.35 (13)	18.04 (10)	65.97 (19)

16.0	9.21 (13)	7.91 (11)	28.00 (16)
24.0	2.20 (40)	1.94 (38)	12.60 (26)
36.0	0[b]	0	0.18 (100)
48.0	0[b]	0	0
AUC_{0-t} (ng*hr/mL)	921.01 (21)	928.86 (20)	979.70 (27)
AUC_{0-inf} (ng*hr/mL)	967.43 (19)	970.84 (21)	1099.24[b] (30)
C_{max} (ng/mL)	167.10 (30)	172.10 (26)	124.78 (34)
T_{max} (hour)	3.42 (58)	2.62 (42)	5.82 (75)
$T_{1/2}$ (hour)	4.00 (41)	4.23 (54)	5.34[b] (52)

a : unless otherwise indicated
b : n = 19

ANOVA was conducted for eachof the pharmacokinetic parameters. Their LS means and ratios of these means are presented below in Table 5:

Table 5 - LS Means and Ratios of LS Means of PK Parameters -- Non-Fasting Study

Treatment	A (Ref-Non-Fasting)	B (Test-Non-Fasting)	C (Test-Fasting)	B / A	B / C
AUC_{0-t} (ng*hr/mL)	921.62	912.29	995.66	0.99	0.92
AUC_{0-inf} (ng*hr/mL)	982.45	948.61	1102.54	0.96	0.86
C_{max} (ng/mL)	163.36	176.25	124.36	1.08	1.42
T_{max} (hour)	3.80	2.18	5.89	0.57	0.37
$T_{1/2}$ (hour)	4.13	4.45	4.91	1.08	0.91

Comments:

1. The calculations for all the pharmacokinetic parameters were confirmed by the reviewer.

2. The test formulation and the reference formulation were absorbed at almost the same rate (mean C_{max}) and to almost the same extent (mean AUC_{0-t} and mean AUC_{0-inf}) under post-prandial condition,.

3. Comparing to administering the test product under fasting condition, the administration of the test product after breakfast increased both mean AUC (5-13%) and mean C_{max} (40%), and the mean T_{max} was shortened by 55% (from 5.8 to 2.6 hours).
4. The ratio of the mean of all three pharmacokinetic parameters for the test product given after food versus reference product given after food were all within the 0.8-1.2 limit.

5. The results of the non-fasting study are acceptable.

Dissolution Testing:

The firm conducted dissolution tests on its glyburide tablets, 1.5 mg and 3 mg, lot #2B001D and #2B002D respectively, compared to the reference products, Glynase^R 1.5 mg tablet and 3 mg tablet respectively. The dissolution method and results are presented below in Table 6.

Table 6 - In Vitro Dissolution Testing

Drug (Generic Name): Glyburide
Dosage Form: Tablet
Dose Strength: 1.5 mg & 3 mg
ANDA No.: 74-792
Firm: Mylan Pharmaceuticals Inc.
Submission Date: 11/21/95

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 75
No. Units Tested: 12
Medium: 0.05 M Borate Buffer, pH 9.5 Volume: 500 mL
Tolerance: NLT (Q) in 45 minutes
Reference Drug: Glynase^R (Upjohn)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 2B002D Strength (mg): 3	Reference Product Lot # 103JC; Exp. 4/97 Strength (mg): 3

	Mean %	Range	%CV	Mean %	Range	%CV
15	102		2.2	104		2.6
30	103		2.4	105		3.0
45	103		2.7	106		2.6
60	103		2.4	105		3.4
Sampling Times (Minutes)	Test Product Lot # 2B001D Strength (mg): 1.5			Reference Product Lot # 671JF; Exp. 9/97 Strength (mg): 1.5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	101		3.1	100		1.9
30	103		2.5	102		1.7
45	102		2.9	103		1.7
60	103		2.6	103		2.0
Content uniformity: test product (3 mg tablets): 100.5%, range of 95.7-103.3% and CV of 2.3% reference product (3 mg tablets): 101.7%, range of 99.5-100.3%, CV of 2.4%						

Comment:

The dissolution method and results comply with those specified in the *Guidance: Glyburide Tablet, In vivo Bioequivalence and In Vitro Dissolution Testing*, issued by the Agency on 04/23/93.

Waiver Request for Glyburide 1.5 mg Tablet:

The firm is requesting a waiver of *in vivo* bioavailability study for the firm's Glyburide 1.5 mg tablet based on the results of bioequivalence studies conducted above on the 3 mg product. The comparative formulations of both strengths of products listed below in Table 7 indicate that both strengths are proportionally similar in its active and inactive ingredients.

Table 7: Comparative Quantitative Composition of Mylan's 1.5 mg and 3 mg Glyburide Tablets

ingredient	1.5 mg tablet	3 mg tablet
	mg/tablet (% of total weight)	
Glyburide, micronized	1.5 (0.83)	3 (1.67)

Lactose, Anhydrous Magnesium Stearate/ Sodium Lauryl Sulfate (94/6) Croscarmellose Sodium Colloidal Silicon Dioxide Pregelatinized Starch D&C Yellow #10		
Total weight	180.00 (100)	180.00 (100)

Comment:

The waiver of *in vivo* bioavailability study for the firm's Glyburide 1.5 mg tablet can be granted per 21 CFR section 320.22(d)(2) since it is proportionally similar in its active and inactive ingredients to the 3 mg tablet and the *in vitro* dissolutions testings are acceptable.

Recommendation:

1. Both fasting and non-fasting bioequivalence studies conducted by Mylan Pharmaceuticals Inc. on its Glyburide 3 mg tablet, lot #2B002D, comparing to Glynase^{R} 3 mg tablet, manufactured by The Upjohn Company have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Mylan's glyburide 3 mg tablet is bioequivalent to the reference product, Glynase^{R} 3 mg tablet manufactured by The Upjohn Company when administered under either fasting or non-fasting condition.

2. The dissolution tests conducted by Mylan Pharmaceuticals Inc. on both of its 1.5 mg and 3 mg glyburide tablets, lot #2B001D and lot #2B002D respectively, have been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of borate buffer, pH 9.5 at 37° using USP 23 apparatus 2 (paddle) at 75 rpm. The test products should meet the following specifications:

   Not less than , of the labeled amount of glyburide in the dosage form is dissolved in 45 minutes.

3. The waiver of in vivo bioequivalence study requirements for the firm's glyburide 1.5 mg tablet is granted per 21 CFR section 320.22(d)(2). The 1.5 mg tablet of the test product will therefore be deemed bioequivalent to Glynase^{R} 1.5 mg, manufactured by The Upjohn Company.

F. Chuang 6/18/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG F.C. Huang 6/18/96

Concur: _____ Date: 6/20/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-792 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Chuang), Drug File, Division File

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